GLP-1 receptor activation in the nucleus accumbens shell regulates oxycodone-mediated behaviors

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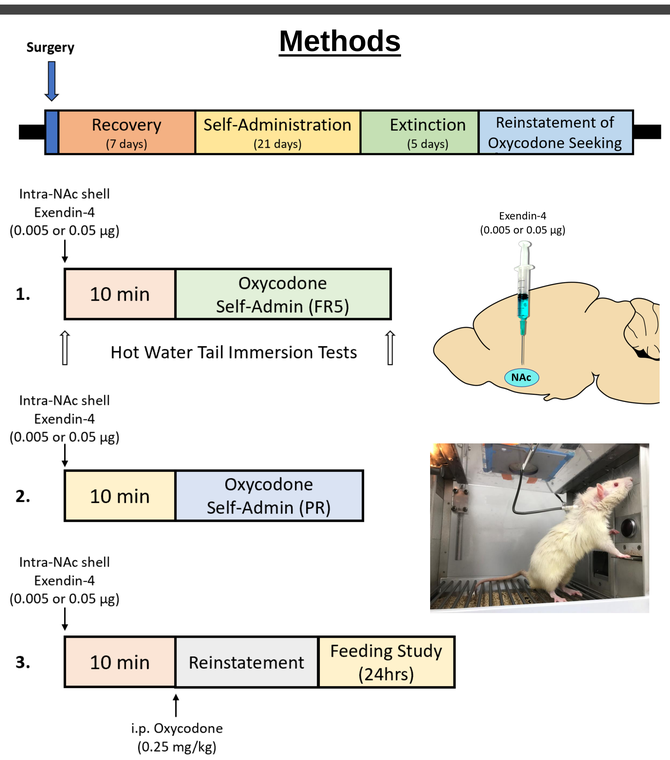
Introduction

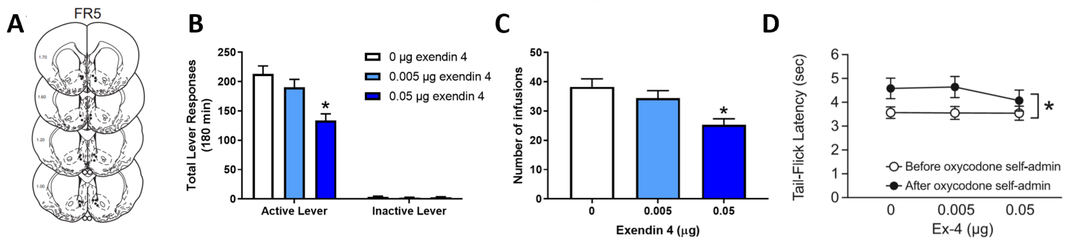
While prescription opioid analgesics are effective for treating nociceptive and inflammatory pain, long-term use of these medications may lead to opioid use disorders and in some cases fatal overdose. Thus, there is a critical need for research aimed at identifying novel pharmacotherapies to treat opioid use disorder including adjunct medications that augment opioid-induced analgesia and reduce the abuse liability of these drugs. A growing body of literature indicates that glucagon-like peptide-1 (GLP-1) receptor agonists reduce drug reinforcement in animal models of addiction.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced by intestinal endocrine L-cells and preproglucagon neurons in the nucleus tractus solitarius of the hindbrain[1,2]. Recent preclinical studies demonstrate that systemic administration of the GLP-1 receptor agonist exendin-4 attenuates cocaine self-administration in mice[3] and cocaine priming-induced reinstatement of drug-seeking behavior in rats[4]. However, no studies to date have examined the efficacy of GLP-1 receptor agonists to reduce opioid-taking and -seeking behaviors. Thus, the goal of this study is to determine if activation of GLP-1 receptors in the nucleus accumbens reduces oxycodone-mediated behaviors and characterized GLP-1R-expressing neurons in the NAc to identify striatal microcircuits underlying the effects of exendin-4 on drug taking.

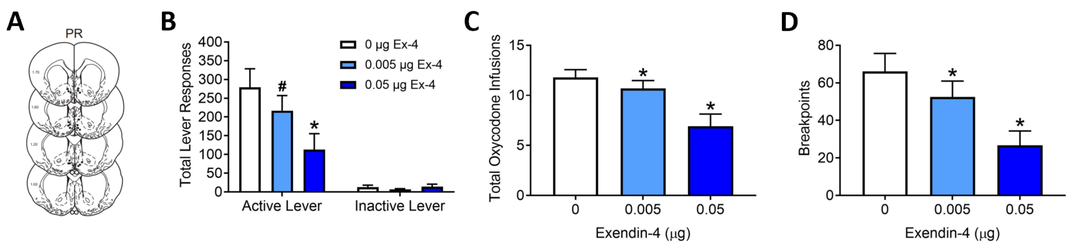
Methods



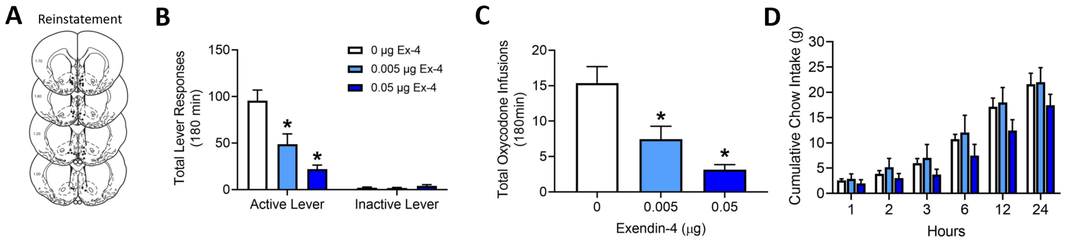
1. Administration of exendin-4 into the NAc shell reduces oxycodone reinforcement without affecting thermal nociception



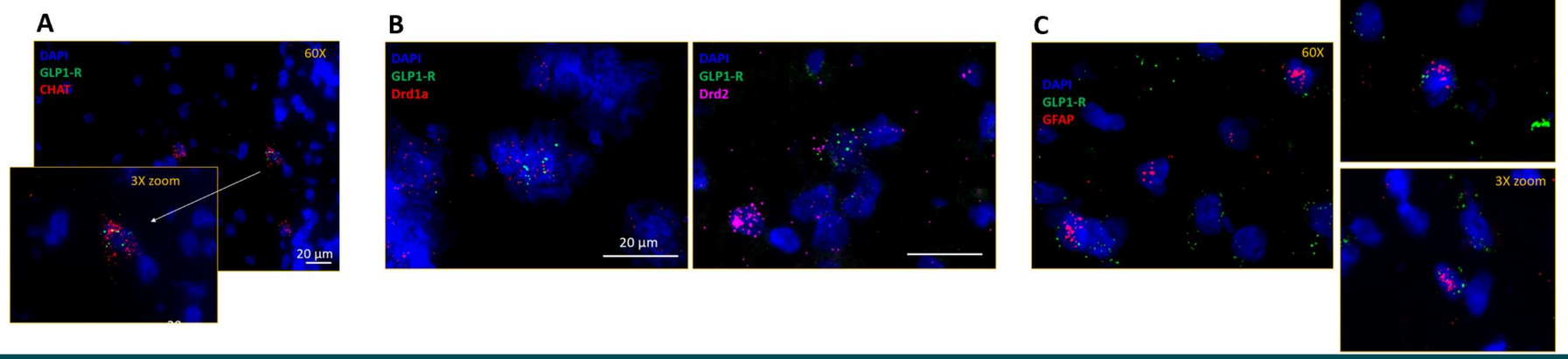
2. Activation of GLP-1Rs in the NAc shell reduces motivation to self-administer oxycodone



3. Intra-accumbens exendin-4 administration reduces the reinstatement of oxycodone seeking without affecting food intake



4. GLP-1 receptors are expressed on cholinergic interneurons, D1R- and D2R-MSNs, and astrocytes in the NAc shell



Summary & Conclusions

- Intra-accumbens administration of the GLP-1R agonist exendin-4 attenuates oxycodone taking- and seeking-behaviors in rats.
- The behaviorally relevant doses of exendin-4 did not produce adverse feeding effects or compromise oxycodone's anti-nociceptive effects in opioid-dependent rats.
- GLP-1 receptors in the nucleus accumbens are expressed on cholinergic interneurons, D1R- and D2R-expressing medium spiny neurons, and astrocytes.
- Together, these findings suggest that GLP-1 receptors may potentially serve as molecular targets to reduce opioid abuse liability.
- Future experiments will examine whether GLP-1R knockdown in NAc cholinergic interneurons blocks the suppressive effects of GLP-1R agonists on opioid taking and seeking.

References

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